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(72) Inventor MAURICE WARD GITTOS

(19)

(54) PREPARATION OF FUSED-RING PYRIDINE AND PYRAZINE DERIVATIVES

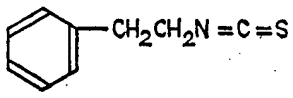
(71) We, ASPRO-NICHOLAS LIMITED, a British Company, of 225 Bath Road, Slough, Buckinghamshire, England, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to compounds having as a substituent on an aromatic nucleus an N-alkylene-thiomidate

(i.e. —C(S—alkyl)=N—alkylene—)

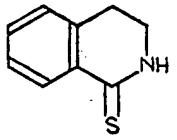
group or a selenium or tellurium analogue thereof. In particular, the invention provides a novel process for the preparation of such compounds in which the N-alkylene imino moiety constitutes part of a dihydropyridine or tetrahydropyrazine ring fused to an aromatic nucleus.

Compounds having an N-alkylene-thioimidate groups are useful intermediates for the preparation of *inter alia* amidino compounds, many of which amidino compounds are pharmaceutically active. In particular, as disclolsed in our U.K. Patent Specification No. 1,244,501, certain 1-alkylthio-3,4-dihydroisoquinolines (i.e. 1-alkylthio-3,4-dihydro-benz[c]-pyridines) may be reacted in manner known *per se* with amines to form 1-amino-3,4-dihydroisoquinolines having cardiovascular activity. Previously, the 1-alkylthio-3,4-dihydroisoquinoline reactants have been prepared *inter alia* from a phenethyl isothiocyanate of formula i



(i)

or a substituted derivative thereof by, as a first stage, heating with a Friedel-Crafts catalyst, for example $AlCl_3$ or H_3PO_4, to form a 1,2,3,4-tetrahydroisoquinoline-1-thione of formula ii

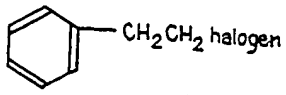


(ii),

or substituted derivative thereof and thereafter reacting the thione with a suitable alkylating agent, for example an alkyl halide, sulphate or sulphonate. The thione is obtained in low yield and therefore it often is necessary to use relatively high temperatures, for example of the order of 200°C, and lengthy reaction times, for example of the order of 24 hours, to obtain a useful yield.

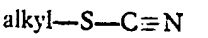
[*Price 25p*]

It has been proposed by Lora-Tamayo *et al* (see Advances in Heterocyclic Chemistry, Katritzky and Boulton, Volume 6, 1966, pages 112—114) to prepare 1-alkylthio-3,4-dihydro-isoquinolines by heating together a β-halogenoalkylbenzene of formula iii



(iii),

or a substituted derivative thereof, and a thiocyanate of formula iv



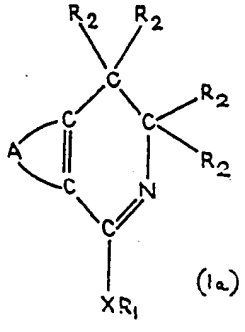
(iv),

in the presence of stannic chloride. Unfortunately, the process has to be carried out in the absence of a solvent and is difficult to control. It is therefore not suitable for commercial scale preparations.

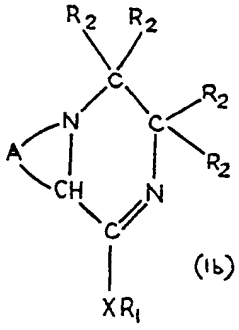
The inventor has found that 1-alkylthio-3,4-dihydroisoquinolines can be prepared in good yields directly from 2-phenethyl isothiocyanates by contacting the isothiocyanate with an alkyl carbonium ion. He has found also that the process has application to the formation of analogous compounds in which the fused benzene ring of the dihydroisoquinoline nucleus is replaced by another aromatic ring system. Further, the process is applicable to the preparation of analogous compounds in which the alkylthio group is replaced by a selenium or tellurium analogue thereof.

The improvement of yield resultant upon using the process of the present invention is illustrated by comparing the cyclisation of 2-phenylisobutylisothiocyanate using the known Friedel-Crafts cyclisation *supra* with that using the novel process of the present invention (see Example 6 herein). Thus, when the said isothiocyanate was heated with $AlCl_3$, 4,4-dimethyl-1,2,3,4-tetrahydro-isoquinoline-1-thione could not be obtained in yields of more than 10% even after several modifications of the standard reaction procedure. The yield could be increased to 65% by using polyphosphoric acid instead of $AlCl_3$ and heating the reaction mixture at 200°C for 24 hours. However, heating the said polyphosphoric acid-containing reaction mixture at 150°C for 10 hours failed to give any yield at all. In comparison, when the isothiocyanate was refluxed at 40°C with triethyloxonium fluoroborate in methylene chloride for 1 hour, 1-ethylthio-4,4-dimethyl-3,4-dihydroisoquinoline was obtained directly in a yield of 80%.

According to the present invention, there is provided a process for preparing an aromatic[c]-dihydro-pyridine or an aromatic[c]-tetrahydro-pyrazine which is substituted in the 1-position by an alkylthio group or a selenium or tellurium analogue thereof of formula Ia or Ib:—



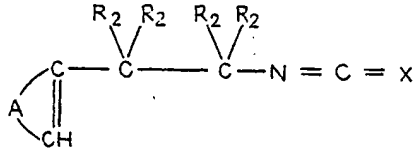
(Ia)



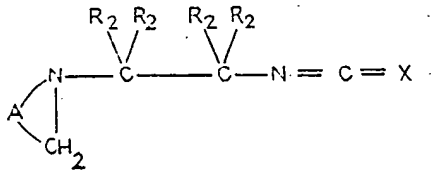
(Ib)

wherein A represents the residue of an aromatic compound of which the pair of adjacent ring atoms shown form part of an aromatic ring; R_1 represents an alkyl (as hereinafter defined) group; each R_2 independently represents a hydrogen atom or a substituent atom or group or together with another R_2 represent a divalent group; and X represents a sulphur, selenium or tellurium atom; which comprises contacting a 2-aromatic-ethyl isocyanate sulphur, selenium or tellurium analogue having an un-

substituted ring carbon atom adjacent to the ring atom attached to the ethyl isocyanate analogue group of formula IIa or IIb:—



IIa



IIb

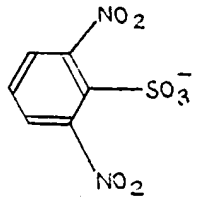
where A, R_2 and X are as defined above with a compound capable of providing an alkyl carbonium ion R_1^+ under the reaction conditions employed.

Unless otherwise stated or clearly implied, the term "alkyl" is used in this Specification, including the claims thereof, to mean a straight, branched or cyclic alkyl group which optionally bears a substituent atom or group.

The process of the present invention is of general application to reactants of the classes specified but, as with most if not all chemical reactions of general application, there will be reactants or combinations of reactions which will not undergo the desired reaction. In particular, if a reactant has a site which is more active under the reaction conditions than the site required for the desired reaction, reaction will occur at said more active site in preference to, and possibly to the exclusion of, reaction at the desired site. Further, the presence of certain substituent atoms or groups in a reactant molecule may so alter the electron density at the desired reaction site that reaction is not longer possible, at least in commercially viable yields. Additionally, the presence of substituent atoms or groups may sterically hinder the desired reaction. These and other factors may prevent use of certain reactants or combination of reactants in the process of the present invention and as far as possible account should be taken of this when selecting the reactants.

The process involves attack at the nucleophilic site of the X atom by a positive ion and hence all other sites in the reactants should be less nucleophilic than that of the X atom. Thus, for example, the reactants generally should not contain a pyridine or imidazole ring because of the high nucleophilic activity of the ring nitrogen atom or bear an amino, hydrazino or amido group. However, such rings or substituent groups may be present if their nucleophilic activity is reduced to a level below that of the X atom by, for example, quaternisation of the nitrogen atom. The extent of nucleophilic activity at any particular site in a reactant molecule is dependent upon both the atom or group occupying that site and the location of the site within the molecule. Therefore, the comparison of nucleophilic activity between the X atom of the isocyanate reactant and any other site in the reactants must be made having regard to the molecule in which the site exists. Further, the reaction relies upon a sufficient electron density at the unsubstituted ring carbon atom adjacent to the ring atom of the isocyanate reactant to which the ethyl isocyanate analogue group is attached. Accordingly, the isocyanate reactant must not bear an electron withdrawing group of sufficient strength and so located in the molecule that the electron density at said unsubstituted carbon atom is reduced to a level at which the desired reaction no longer occurs. The minimum level of electron density required cannot be defined in general terms but it is below the normal level of the methylidyne (i.e. —CH=) groups in an unsubstituted benzene ring.

Alkyl carbonium ions are positively charged intermediates formed by the removal of a pair of electrons from a carbon atom of a monovalent aliphatic hydrocarbon radical. They have only a transient existence as such but do exist in solvated form such as in trialkyloxonium (i.e. $(R_1)_3O^+$) and dialkoxycarbonium (i.e. $HC^+(OR_1)_2$)ions. Conveniently such solvated ions are supplied to the reaction mixture in combination with such non-nucleophilic anions as BF_4^-;



$AuCl_4^-$; $AlCl_4^-$; $SbCl_6^{--}$; $FeCl_4^-$; and $PtCl_6^{--}$;

Another suitable source of alkyl carbonium ions are the alkyl esters of certain strong acids such as fluorosulphonic acid (FSO_3H) and perfluorinated alkyl sulphonic acids especially CF_3SO_3H, $C_4F_9SO_3H$. A preferred class of compounds capable of providing an alkyl carbonium ion are the trialkyloxonium tetrafluoroborates.

The radical from which the incipient carbonium ion R_1^+ is derived may be a straight or branched chain or cyclic alkyl radical. Said radical may bear a substituent atom or group which permits of formation of an alkyl carbonium ion and is inert under the reaction conditions in that it does not prevent formation of the desired alkylenethioinidate or analogous seleno or telluro substituent on the aromatic reactant. Preferably, the carbonium ion R_1^+ contains 1 to 6 carbon atoms. An especially preferred class of alkyl carbonium ions are those derived from unsubstituted alkyl groups containing from 1 to 4 carbon atoms, i.e. methyl, ethyl, propyl and butyl. Where as above and elsewhere in this specification, reference is made to a substituent without specifying its isomeric state, that substituent includes all its isomers singly and in admixture. Thus for example reference as above to butyl includes *n*-, *iso*, *s*- and *tert*-butyl.

The isocyanate reactant may be carbocyclic or, subject to the proviso that no ring hetero-atom is as nucleophilic as the X-atom in the appropriate isocyanate reactant, heterocyclic and may have an aromatic nucleus constituted by a single ring or fused ring system. Examples of suitable aromatic nuclei include those of benzene, naphthalene, thiophen, pyrrole and indole. When the aromatic nucleus contains an imino nitrogen atom, e.g. pyrrole and indole, the ethyl isocyanate analogue group can be attached to said nitrogen atom or to any of the ring carbon atoms.

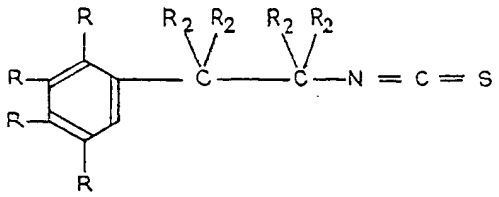
The nucleus of the isocyanate reactant may bear one or more substituents. Such substituents must be inert under the reaction conditions in that they do not prevent the desired reaction from taking place. Thus, as explained above, they must be less nucleophilic in the molecule than the X-atom in the appropriate isocyanate reactant and must not sterically hinder the desired reaction. Further, if they are electron-withdrawing in nature they may not occupy a position in the molecule which will reduce the electron density of the reactive unsubstituted ring carbon atom to an inactive level. Examples of substituent atoms or groups which may be present on the aromatic nucleus are halogen atoms; alkyl groups optionally substituted by one or more alkoxy, halogen or phenyl; alkoxy groups; cycloalkyl groups; alkylenedioxy; and phenyl optionally substituted by one or more alkyl, alkoxy or halogen. Preferably any or each alkyl group or alkyl moiety contains from 1 to 6 carbon atoms. Specific examples of suitable substituents are fluorine, chlorine, bromine, iodine, methyl, ethyl, propyl, butyl, pentyl, hexyl, 2-methoxy-ethyl, ethoxymethyl, 4-methoxybutyl, 2-chloroethyl, 2-iodoethyl, 2-bromoethyl, 2-fluoroethyl, 2-chloropropyl, 3-fluoropropyl, trifluoromethyl, trichloromethyl, 5-bromopentyl, 3-methyl-5-iodopentyl, benzyl, methoxy, ethoxy, butoxy, hexyloxy, cyclopropyl, cyclobutyl, cyclohexyl, methylenedioxy, phenyl, tolyl, 1-ethoxyphenyl, 3-propoxyphenyl, 1-chlorophenyl and 2-bromophenyl.

Each methylene group of the ethyl isocyanate analogue group may be substituted by one or more atoms or groups represented in formula I by R_2 which are inert under the reaction conditions in that they do not prevent the desired reaction from taking place. Thus as explained above, they must be less nucleophilic in the molecule than the X-atom in the isocyanate analogue grouping and must not sterically hinder the desired reaction.

Examples of suitable R_2 atoms and groups are hydrogen; alkyl groups optionally substituted by one or more alkoxy, halogen or phenyl; alkoxy groups; and phenyl optionally substituted by one or more halogen, alkyl or alkoxy. Alternatively, two R_2 symbols may together represent an alkylene group which with the adjacent ring carbon atom or atoms constitutes a cycloalkyl group. Preferably any or each alkyl group or moiety contains 1 to 6 carbon atoms. Specific examples of suitable R_2 atoms and groups are methyl, ethyl, propyl, butyl, hexyl, 2-methoxy-ethyl, ethoxy-

methyl, 4-methoxybutyl, 2-chloroethyl, 2-iodoethyl, 2-bromoethyl, 2-fluoroethyl, 2-chloropropyl, 3-fluoropropyl 5-bromopentyl, 3 - methyl - 5 - iodopentyl, benzyl, methoxy, ethoxy, butoxy, hexyloxy, cyclopropyl, cyclobutyl, cyclohexyl, phenyl, tolyl, 1-ethoxyphenyl, 3-propoxyphenyl, 1-chlorophenyl and 2-bromophenyl.

A preferred class of isocyanate reactant is constituted by those compounds of formula III:—



wherein each R independently represents hydrogen; halogen; C_1—C_6 alkyl optionally substituted with halogen; or C_1—C_6 alkoxy, or a pair of adjacent R symbols represent C_1 or C_2 alkylenedioxy group, and each R_2 independently represents hydrogen; C_1—C_6 alkyl optionally substituted with halogen; phenyl optionally substituted with halogen, C_1—C_6 alkyl or C_1—C_6 alkoxy; or phenyl substituted C_1—C_6 alkyl potionally substituted in the phenyl moiety with halogen, C_1—C_6 alkyl or C_1—C_6 alkoxy.

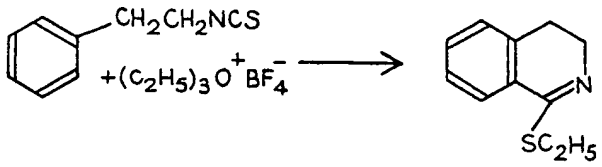
The reaction of the invention may be performed by mixing the reactants in the presence or absence of an inert solvent at ambient or elevated temperatures. A suitable temperature range is from 20° to 150°C, more especially 40—100°C, and suitable solvents include chloroform, methylene chloride and diethylsulphate. When using a solvent having its boiling point within the said range, it is preferred to reflux the reactant mixture.

The 1-substituted-3,4-dihydro-aromatic[c] pyridines prepared by the process of the present invention are valuable chemical intermediates in the preparation of, for example, the corresponding 1-amino compounds. In particular, the 1-alkyl-thio, -seleno, or -telluro-3,4-dihydroisoquinolines are intermediates in the preparation of pharmaceutically active 1-amino-3,4-dihydroisoquinolines as described in U.K. Patent No's 1,244,501 (Aspro-Nicholas) and 1,264,485 (Rhone-Poulenc). Accordingly, the present invention provides also a method of preparing 1-amino-3,4-dihydro-aromatic[c] pyridines which comprises preparing the corresponding 1-alkylthio, -seleno, or -telluro-3,4-dihydro-aromatic[c]pyridine by the novel process previously described and then reacting said intermediate with an amine in manner known *per se*. In a preferred embodiment of this two stage process, 1-amino-3,4-dihydroisoquinolines are prepared by first preparing the corresponding 1-alkyl-thio, -seleno, or -telluro-3,4-dihydro-isoquinoline by the novel process and then reacting said intermediate with the corresponding amine. The reaction parameters required for the second stage of said two stage processes are set forth in the specifications of the aforementioned U.K. Patents.

The following Examples illustrate the present invention:—

Example 1

Preparation of 1-ethylthio-3,4-dihydroisoquinoline



2-Phenylethyl isothiocyanate (132.7 g; 0.82 mole) was added dropwise to a stirred solution of triethyloxonium tetrafluoroborate (190 g; 1 mole) in anhydrous methylene chloride (350 ml.). The solution was heated under reflux for half an hour, the methylene chloride evaporated off and the residue heated at 100°C for one hour during which time ether distilled off.

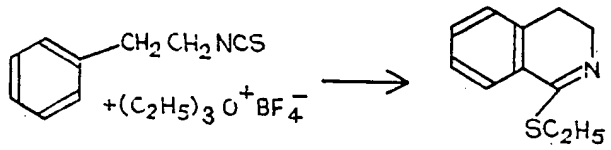
The cooled residue was basified by the addition of 2N sodium hydroxide, the oily layer extracted with ether and the ethereal solution washed with 5N hydrochloric acid (250 ml). Basification of the acidic aqueous extract with 5N sodium hydroxide liberated an oily base which was isolated by ether extraction. Distilla-

tion of the dried ($MgSO_4$) ether extract gave 1-ethylthio-3:4-dihydroisoquinoline b.p. 109—111°C/0.7 mm (135 g; 87%).

Example 2

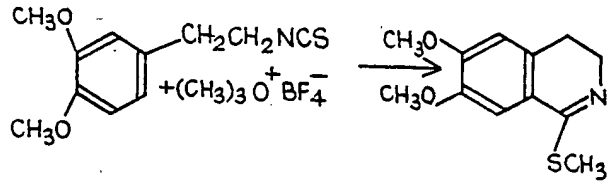
Preparation of 1-ethylthio-3,4-dihydroisoquinoline

2-Phenylethyl isothiocyanate (16.3 g; 0.1 mole) in diethyl sulphate (30 ml) was added to a stirred solution of triethyloxonium tetrafluoroborate (19 g; 0.1 mole) in diethylsulphate (50 ml) and the temperature of the mixture gradually raised to 110°C where it was held for 1½ hours. Ether was distilled off during this period. The diethyl sulphate was distilled off under reduced pressure and the cooled residue treated with dilute sodium hydroxide (2N). The oil was separated off using ether as solvent and the ethereal solution extracted with 2.5N hydrochloric acid. Basification of the acidic aqueous extract with 5N sodium hydroxide liberated as an oil 1-ethylthio-3,4-dihydroisoquinoline b.p. 109—111°C/0.7 mm (14 g. 73%).



Example 3

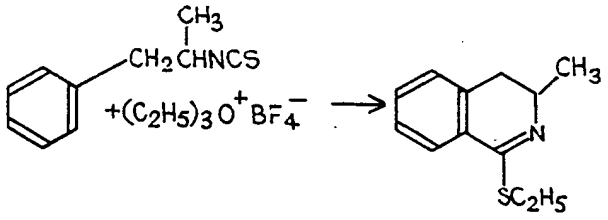
Preparation of 1-methylthio-6,7-dimethoxy-3,4-dihydroisoquinoline



A mixture of 2-(3:4 dimethoxyphenyl) ethyl isothiocyanate (6.69 g; 0.03 mole) and trimethyloxonium tetrafluoroborate (4.44 g; 0.03 mole) in chloroform (50 ml) was refluxed with stirring for 1½ hours. The chloroform was evaporated and the residue treated with 2.5N sodium hydroxide solution. The product 1-methylthio-6:7-dimethoxy-3:4-dihydroisoquinoline (5.5 g 77.5%) was liberated as an oil which slowly crystallised to a solid m.p. 94—6°C.

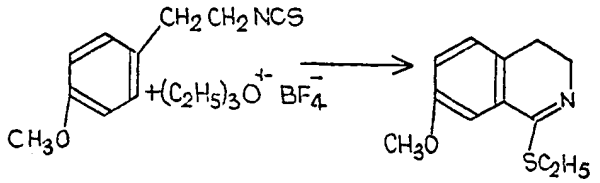
Example 4

Preparation of 1-ethylthio-3-methyl-3,4-dihydroisoquinoline



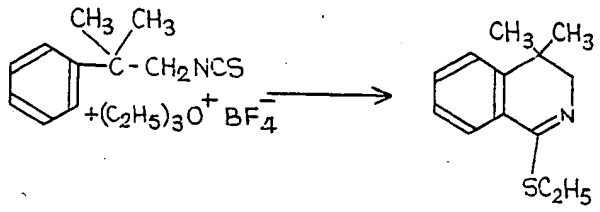
d-2-Phenylisopropyl isothiocyanate (142.7 g; 0.8 mole) was added in a thin stream to a rapidly stirred solution of triethyloxonium tetrafluoroborate (171 g; 0.9 mole) in anhydrous methylene chloride (350 ml). The stirred mixture was refluxed for one hour, the solvent evaporated and the residue heated on a boiling bath with stirring. Ether was evolved and the mixture gradually solidified. The cooled solid was triturated with dry ether and the crystalline d-1-ethylthio-3-methyl-3:4-dihydroisoquinoline tetrafluoroborate was filtered off and dried (231 g; 97.5%).

Example 5
Preparation of 1-ethylthio-7-methoxy-3,4-dihydroisoquinoline



2-(4-Methoxyphenyl)ethylisothiocyanate (28 g. 0.145 mole) was mixed with triethyloxonium tetrafluoroborate (0.145 mole) in anhydrous methylene chloride (20 ml) and the solution refluxed for one hour. After evaporation of the methylene chloride the cooled residue was treated with water (100 ml) and 5N sodium hydroxide until strongly alkaline. Basic material was extracted with ether and back extracted with dilute hydrochloric acid. The acid solution was basified with sodium hydroxide and the organic base isolated by ether extraction. Distillation of the dried ether solution gave 1-ethylthio-7-methoxy-3:4-dihydroisoquinoline as an oil (24 g; 75%).

Example 6
Preparation of 1-ethylthio-4,4-dimethyl-3,4-dihydroisoquinoline



Phenylisobutyl isothiocyanate (31.5 g; 0.165 mole) was added dropwise to a stirred solution of triethyloxonium tetrafluoroborate (32 g) in anhydrous methylene chloride (100 ml). The solution was heated under reflux for 1 hour, the methylene chloride evaporated off and the residue heated at 100°C for 1 hour during which time ether distilled off. The cooled residue was basified by the addition of 2N sodium hydroxide, the oily layer extracted into ether and the ethereal solution washed with 5N hydrochloric acid. Basification of the acidic aqueous extract with 5N sodium hydroxide liberated an oily base which was isolated by ether extraction. Distillation of the dried solution gave 1-ethylthio-4:4-dimethyl;3:4-dihydroisoquinoline as an oil (29 g; 80%).

The following comparative Examples 6A and 6B illustrate the improved yield obtainable by the process of the present invention when using 2-phenylisobutylisothiocyanate as starting material.

Example 6A (comparative)
Cyclisation with aluminium trichloride

Anhydrous aluminium trichloride (6.7 g, 0.05 mole) was added during 2 hours to a solution of phenylisobutylisothiocyanate (4.75 g, 0.025 mole) in trichloroethylene (5 ml) whilst stirring at 0°C. The resulting yellow slurry was stirred for 8 hr at 0°C but, on warming to room temperature for the work-up, the mixture blackened. The product was extracted with ether after evaporation of the solvent from the reaction mixture. Concentration of the ether layer gave a black tar which was chromatographed on silica using chloroform light petroleum (20:80) as the eluent. A yellow crystalline solid was obtained (4,4-dimethyl-1,2,3,4-tetrahydroisoquinoline 1-thione), m.p. 108°C (Yield 0.4 g).

Other Lewis acids were used in an exactly similar way to that described above. With $SnCl_4$ the yield was 0.4 g and with BF_3, the yield was 0.9 g.

Example 6B
Cyclisation with polyphosphoric acid (PPA)

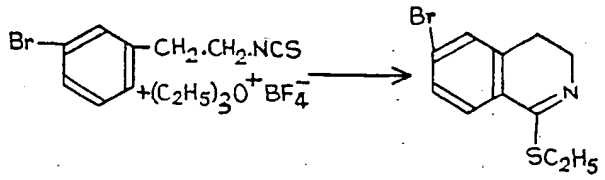
PPA (47 g) was stirred at 200°C and phenylisobutylisothiocyanate (4.75 g) added over 30 min. Stirring was continued at this temperature for 20 hours and then the mixture was cooled. It was poured into water (100 ml) and the dark oil which

separated was extracted with ether and dried ($MgSO_4$). Concentration of the ether layer gave a black solid, which was triturated with light petroleum to give a yellow solid, m.p 100°C (Yield 3.0 g).

Less severe conditions than those described above (i.e. 100° for 10 hours; 150° for 10 hours) failed to give any of the cyclised product.

Example 7

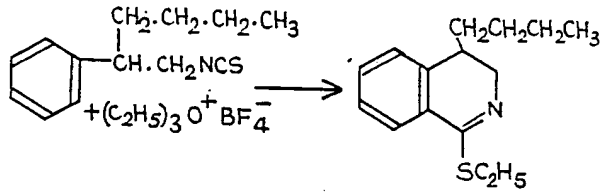
Preparation of 1-ethylthio-6-bromo-3,4-dihydroisoquinoline



The process of Example 2 was repeated using 2-(*m*-bromo-phenyl) ethyl isothiocyanate as the isocyanate reactant to yield 1-ethylthio-6-bromo-3,4-dihydroisoquinoline b.p. 126—9°C/0.1 mm (56.5% yield).

Example 8

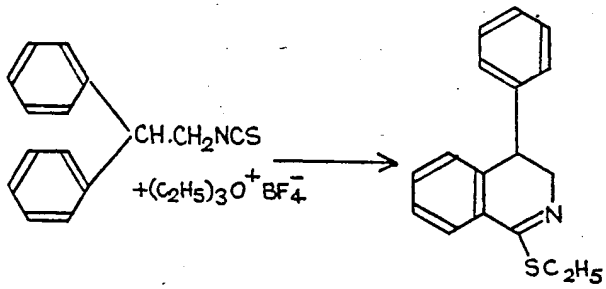
Preparation of 1-ethylthio-4-*n*-butyl-3,4-dihydroisoquinoline



The process of Example 2 was repeated using 2-phenyl-*n*-hexyl isothiocyanate as the isocyanate reactant to yield 1-ethylthio-4-butyl-3,4-dihydroisoquinoline b.p. 122—4°/0.2 mm (72% yield).

Example 9

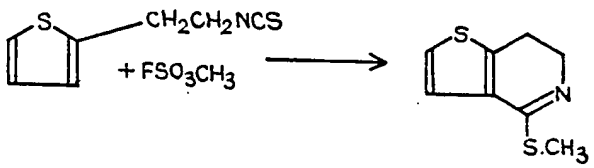
Preparation of 1-ethylthio-4-phenyl-3,4-dihydroisoquinoline



The process of Example 2 was repeated using 2,2-diphenyl-ethyl isothiocyanate as the isocyanate reactant to yield 1-ethylthio-4-phenyl-3,4-dihydroisoquinoline b.p. 161°C/0.15 mm (55% yield).

Example 10

Preparation of 1-methylthio-3,4-dihydro(thieno[3,2-a] pyridine fluorosulphonate



2-Thien-2'-yl ethyl isothiocyanate (0.8 mole) was added slowly to a rapidly stirred solution of methyl fluorosulphonate (0.8 mole) in anhydrous methylene chloride (350 ml). The stirred mixture was refluxed for one hour, the solvent evaporated and the residue heated on a boling water bath whilst stirring. The mixture gradually solidified to 1-methylthio-3,4-dihydro (thieno[3,2-c]) pyridine fluorosulphonate. After purification the said salt had a melting point of 191°C and was present in a yield of 62%.

WHAT WE CLAIM IS:—

1. A process for preparing an aromatic[c]dihydro-pyridine or aromatic[c]tetrahydro pyrazine of formula Ia or Ib herein, wherein A represents the residue of an aromatic compound of which the pair of adjacent ring atoms shown form part of an aromatic ring; X represents sulphur, selenium or tellurium; R_1 represents an alkyl (as hereinbefore defined) group; and each R_2 individually represents a hydrogen atom or a substituent atom or group or together with another R_2 represent a divalent group, which comprises contacting a 2-aromatic-ethyl isocyanate sulphur, selenium or tellurium analogue of formula IIa or IIb herein, wherein X_1, R_2 and A are as defined above, with a compound capable of providing an alkyl carbonium ion R_1^+ under the reaction conditions employed.

2. A process as claimed in Claim 1 wherein each R_2 individually represents hydrogen, alkyl optionally substituted by one or more alkoxy, halogen or phenyl; alkoxy; or phenyl optionally substituted by one or more alkoxy, halogen or alkyl, or together with another R_2 represents alkylene which constitutes with the adjacent ring carbon atom or atoms a cycloalkyl group.

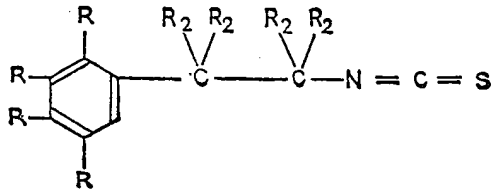
3. A process as claimed in Claim 2 wherein the alkyl moiety of any group represented by R_2 contains from 1 to 6 carbon atoms.

4. A process as claimed in Claim 2 wherein each R_2 individually represents hydrogen, methyl or methoxy.

5. A process as claimed in any one of the preceding Claims wherein the aromatic ring is benzene, naphthalene, thiophen, pyrrole or indole.

6. A process as claimed in Claim 5 wherein the product is a 1-alkylthio-3,4-dihydroisoquinoline.

7. A process as claimed in Claim 6 wherein the isocyanate reactant has the formula

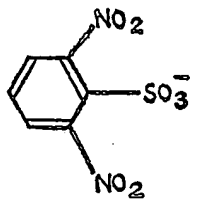


wherein each R independently represents hydrogen, halogen, C_1—C_6 alkyl optionally substituted with halogen; or C_1 to C_6 alkoxy; or together with an adjacent R represents C_1 or C_2 alkylenedioxy, and each R_2 independently represents hydrogen; C_1—C_6 alkyl optionally substituted with halogen; phenyl optionally substituted with halogen, C_1—C_6 alkyl or C_1—C_6 alkoxy; or phenyl substituted C_1—C_6 alkyl optionally substituted in the phenyl moiety with halogen, C_1—C_6 alkyl or C_1—C_6 alkoxy.

8. A process as claimed in any one of the preceding Claims wherein the compound capable of providing an alkyl carbonium ion is a salt of the solvated alkyl carbonium ion with a non-nucleophilic anion.

9. A process as claimed in Claim 8 wherein the solvated ion is a trialkyloxonium or dialkoxy carbonium ion.

10. A process as claimed in Claim 8 or Claim 9 wherein the anion is BF_4^-



$AuCl_4^-$, $AlCl_4^-$, $SbCl_6^{--}$, $FeCl_4^-$ or $PtCl_6^{--}$.

11. A process as claimed in Claim 10 wherein the compound capable of providing an alkyl carbonium ion is a trialkyl-oxonium tetrafluoroborate.

12. A process as claimed in any one of Claims 1 to 7 wherein the compound capable of providing an alkyl carbonium ion is an alkyl ester of a strong acid.

13. A process as claimed in Claim 12 wherein the strong acid is fluorosulphonic acid or a perfluorinated alkyl sulphonic acid.

14. A process as claimed in any one of the preceding Claims wherein the alkyl carbonium ion R_1^+ is derived from a straight or branched chain unsubstituted C_1—C_6 alkyl group.

15. A process as claimed in Claim 14 wherein the alkyl carbonium ion is methyl or ethyl carbonium ion.

16. A process as claimed in any one of the preceding Claims wherein the reaction is carried out at a temperature in the range 20° to 150°C.

17. A process as claimed in Claim 16 wherein the temperature is in the range 40 to 100°C.

18. A process as claimed in Claim 16 or Claim 17 wherein the reaction is carried out in a solvent under reflux conditions.

19. A process as claimed in Claim 18 wherein the solvent is chloroform, methylene chloride or diethylsulphate.

20. A process as claimed in Claim 1 substantially as hereinbefore described in any of the Examples.

21. A 1 - substituted - 3,4 - dihydro - aromatic[c]pyridine whenever prepared by a process as claimed in any one of the preceding Claims.

22. A process for preparing a 1-amino-3,4-dihydroaromatic[c]pyridine which comprises treating a compound as claimed in Claim 21 with an amine in manner known *per se*.

23. A 1 - substituted - aromatic[c]tetrahydro - pyrazine whenever prepared by a process as claimed in any one of the preceding Claims.

24. A process for preparing a 1-amino-aromatic[c]-tetrahydropyrazine which comprises treating a compound as claimed in Claim 21 with an amine in manner known *per se*.

NICHOLAS J. FLOWER,
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